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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/918,407	08/26/97	ROTH J	INGN:050/HYL

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EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	11

DATE MAILED: 11/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/918,407	Applicant(s) Roth et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *Sep 1, 1999*.

☐ This action is **FINAL.**

☒ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-26, 32-61, 77-79, 83-89, 96-101, 111, 112, 115-120, and 127-130* are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-26, 32-61, 77-79, 83-89, 96-101, 111, 112, 115-120, and 127-130* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Applicant's arguments filed September 1, 1999 in Paper No. 10 regarding the rejections of claims 1-26, 32-61, 77-79, 83-89, 96-101, 111-112, 115-120 and 127-130 under 35 USC 103 have been fully considered but they are not persuasive. The response to the arguments is in the repeated rejections below.

2. Applicant's rebuttal regarding the rejection of claim 1 under 35 USC 102 and claims 1-26, 32-61, 77-79, 83-89, 96-101, 111-112, 115-120 and 127-130 under 35 USC 112, first paragraph is found convincing and the rejections are withdrawn.

3. Applicant's amendments to the specification has overcome the rejection of claim 6 under 35 USC 112, second paragraph in the previous office action, and the rejection is withdrawn.

Double Patenting

4. Claims 1-135 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-105 of U.S. Patent No. 5,747,469. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed method of killing a cell, comprising contacting a cell with a p53 gene and a DNA damaging agent contains the same elements as the patented method of US Patent No. 5,747,469. Other common elements of the instant claimed invention and in US Patent No.

5,747,469 are that the p53 gene may be in a viral vector, the p53 gene may be linked to a promoter, and the cells may be various tumor cells. Commonly claimed is a method of killing a tumor cell in a patient in need thereof, comprising administering to said tumor cell a therapeutically effective amount of a viral vector comprising a p53 gene operatively linked to a promoter, and numerous well known DNA damaging agents.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-26, 32-61, 77-79, 83-89, 96-101, 111, 112, 115-120 and 127-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowe et al. or Clarke et al. in view of Tischler et al., Will et al. and Gregory et al.

The claims are drawn to a method of killing a cell comprising contacting a cell with a p53 gene and a DNA damaging agent, where the agent may be X-rays, UV irradiation, gamma irradiation, microwaves, adriamycin, 5-flourouracil, etoposide, campothecin, actinomycin-D, mitomycin C, or cisplatin. The p53 gene may be in a non-viral vector, which may be a naked DNA plasmid or a plasmid in a liposome or in a adenoviral vector. The adenoviral vector may be deleted for one essential gene, which may be the E1A and E1B regions. The cell may be a

human tumor cell. The plasmid may have a cytomegalovirus promoter and an SV40 polyadenylation signal.

Lowe et al. (see the entire article) or Clarke et al. (see the entire article) taught a method of killing a cell comprising contacting a cell with a DNA damaging agent where the combined effect of the p53 gene produced cell death, where the agent may be X-rays, gamma irradiation, or etoposide. The cell may be a human tumor cell.

Lowe et al. or Clarke et al. did not teach that the DNA damaging agent may be UV irradiation, microwaves, adriamycin, 5-flourouracil, campothecin, actinomycin-D, mitomycin C, or cisplatin, nor that the vector may be an adenoviral vector which may be deleted for one essential gene, which may be the E1A and E1B regions, nor that the plasmid may have a cytomegalovirus promoter and an SV40 polyadenylation signal. Also, Lowe et al. and Clarke et al. did not teach that the p53 gene be exogenously introduced into a cell.

Tischler et al. taught that the DNA damaging agent was X-rays, UV irradiation, gamma irradiation, microwaves, adriamycin, 5-flourouracil, etoposide, campothecin, actinomycin-D, mitomycin C, or cisplatin.

Wills et al. (see the entire article) and Gregory et al. (see the entire article) taught that an adenoviral vector expressing the p53 gene may be deleted in E1A or E1B, which contained a CMV promoter.

The use of an SV40 polyadenylation signal sequence and encapsulation of the vector in a liposome are arbitrary choices within the purview of an ordinary skilled artisan and, lacking

unexpected results, are not deemed to make a patentable distinction to the instant claimed invention.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Lowe et al. or Clarke et al. with Tischler et al., Wills et al. and Gregory et al. because they were all investigating the effects of p53 on cell death. Will et al. and Gregory et al. demonstrate the well known use of vectors to introduce wild type and mutant p53 into target cells to investigate the effect of the p53 gene on cell death. Tischler et al. taught the well known DNA damaging agents enumerated in the claims which are demonstrated to interact specifically with p53, affecting the action of p53 in cell death.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Lowe et al. or Clarke et al. with Tischler et al., Will et al. and Gregory et al. because they were all investigating p53 in cells to evaluate the effects of p53 gene on cell death. Lowe et al., Clarke et al. and Tischler et al. showed that the combination of DNA damaging agents with the p53 gene produced cell killing. Tischler et al. provided a larger assortment of obvious DNA damaging agents in combination with the p53 gene. The adenoviral vectors of Will et al. and Gregory et al. demonstrated the well known use of vectors for the purposes of introducing the p53 gene into cells to study cell death. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Lowe et al. or Clarke et al., Tischler et al., Will et al. and Gregory et al.

Response to Arguments

7. Applicants have argued in Paper No. 10 that neither Lowe et al. nor Clarke et al. taught that p53 could be introduced into a cell to induce cell death when combined with a DNA damaging agent.

Lowe et al. in the abstract taught "[t]hese results demonstrate that p53 is required for radiation-induced cell death". Clarke et al. taught in the abstract "[o]ur results show that p53 exerts a significant and dose dependent effect in the initiation of apoptosis, but only when it is induced by agents that cause DNA-strand breakage." These teachings are clear and to the point and instruct one of skill in the art the relationship of p53 and DNA damaging agents in causing cell death. Whether the prior art teaches the introduction of functional genes encoding p53 into a targeted cell is irrelevant, because one of ordinary skill in the art would know that introduction of a functional p53 gene into a target cell would, in fact cause cell death in the presence of DNA damaging agents.

8. Applicant's arguments in Paper No. 10 rely on teachings of Kastan et al. and Stichenmeyer et al. which taught away from the instant claimed invention. These references are not set forth in the rejection, and Kastan et al. and Stichenmeyer et al. in no way negative the teachings of the later published teachings of Lowe et al. and Clarke et al. Since the teachings of Lowe et al. and Clarke et al. clearly taught the combined effect of p53 and DNA damaging agents to cause cell death. The arguments therefore are not deemed persuasive, and the rejection stands.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
November 18, 1999

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER